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10/695,509	10/28/2003	Gary G. Schwartz	SCZ-102	5435
7590	03/22/2007		EXAMINER	
Ted W. Whitlock 5323 SW 38th Avenue Ft. Lauderdale, FL 33312			FETTEROLF, BRANDON J	
			ART UNIT	PAPER NUMBER
				1642
SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE		
3 MONTHS	03/22/2007	PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/695,509	SCHWARTZ ET AL.	
	<b>Examiner</b> Brandon J. Fetterolf, PhD	<b>Art Unit</b> 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 29 January 2007.
- 2a) This action is FINAL.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 20-38 is/are pending in the application.
  - 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 20-38 is/are rejected.
- 7) Claim(s) \_\_\_\_\_ is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.
 

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  - a) All    b) Some \* c) None of:
    1. Certified copies of the priority documents have been received.
    2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
    3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |                                                                                      |                                                                   |
|--------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____.                                     |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____.                                                         | 6) <input type="checkbox"/> Other: _____.                         |

## DETAILED ACTION

### *Response to the Amendment*

The Amendment filed on 1/29/2007 in response to the previous Non-Final Office Action (6/20/2006) is acknowledged and has been entered.

Claims 20-38 are currently pending and under consideration.

(Note: In the response to the Non-Final Office Action (6/20/2006), Applicants filed two claim sets, each of which cancelled claims 1-19 and added new claims 20-38. However, new claims 20 and 27 in each new claim set appear to recite different subject matter. For examination purposes, the claim set entitled "Listing of Claims" will be used.)

### New Rejections Necessitated by Amendment:

#### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 20, 27 and 34 recites the limitation "said 25-dihydroxyvitamin D or its said analog, salt or derivative" in the 4<sup>th</sup> or 5<sup>th</sup> line of the claim. However, while the claims recited 25-dihydroxyvitamin D or an analog, salt, or derivative thereof, there is insufficient antecedent basis for the limitation "said 25-dihydroxyvitamin D or its said analog, salt or derivative" in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would

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result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

**The nature of the invention**

Claims 34-38 are drawn to a method of treating benign prostatic hyperplasia in an animal, comprising an effective amount of 25-hydroxyvitamin D or an analog, salt, or derivative thereof. As such, the invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

**Level of skill in the art**

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

**The breadth of the claims**

Applicants broadly claim a method of treating benign prostatic hyperplasia in an animal, while reducing the risk of UV radiation exposure or vitamin D toxicity, said method comprising the step of administering to the animal a composition comprising an effective amount of 25-hydroxyvitmain D or an analog, salt, or derivative thereof to increase the levels of a metabolite of said 25-dihydroxyvitmain D or its analog, salt or derivative in said cancer cells in a target organ wherein the cancer cells have a hydroxylase enzyme for synthesizing 1,25-dihydroxyvitmain D from said 25-hydroxyvitamin D. As such, the claims imply that there is a correlation between the presence of a hydroxylase enzyme for synthesizing the active 1,25-dihydroxyvitamin D from a metabolic precursor and benign prostatic hyperplasia.

**Guidance in the specification and Working Examples**

The specification teaches that one aspect of the invention comprises increasing the local cellular levels of 1,25(OH)<sub>2</sub>D by administering an effective amount of a Vitamin D metabolite which can be metabolically converted by the target cells to 1,25(OH)<sub>2</sub>D for the prevention or treatment of cell proliferation, invasiveness, or metastasis (page 17, lines 10-15). For example, the specification teaches that the subject method of administering a metabolic precursor of 1,25(OH)<sub>2</sub>D to a patient has been shown to be successful in producing 1,25(OH)<sub>2</sub>D by prostatic cancer cells and two primary culture of cells, NP96-5 and BPH96-11 (page 19, lines 21+). Moreover, the specification teaches that colon or breast cells have also been shown to possess 1 $\alpha$ -OHase activity (page 25, lines 1-2). The specification further teaches that in one embodiment, a polynucleotide construct containing a gene that codes for 1 $\alpha$ -OHase can be used to treat a cell exhibiting benign prostatic hyperplasia. Thus, while the specification teaches that 1 $\alpha$ -OHase which is capable of synthesizing 1,25(OH)2D is present in two prostatic cancer cells lines, 1 BPH cell line and colon/breast cancer cells, the specification appears to be silent on a correlation between the synthesis of 1,25(OH)<sub>2</sub>D from administration of a metabolic precursor and an effective *in vivo* treatment of benign prostate hyperplasia. As such, if there is no correlation then the examples do not constitute working examples. While it is understood that the absence of working examples should never be the sole reason for rejecting a claims as being broader than an enabling disclosure, the criticality of working examples in an unpredictable art, such as the treatment of cancer, is required for practice of the claimed invention.

**Quantity of experimentation**

The quantity of experimentation in the areas of cancer therapy is extremely large given the unpredictability associated with treating cancer in general and the lack of correlation of *in vitro* findings to *in vivo* success, and the fact that no known cure or preventive regimen is currently available for cancer.

**The unpredictability of the art and the state of the prior art**

The state of the art at the time of filing was such that one of skill could recognize that vitamin D3 undergoes hydroxylation first in the liver to form 25-hydroxyvitamin D3 which is further hydroxylated in the kidney by Vitamin D 1a-hydroxylase to create the biologically active form 1,25 (OH)<sub>2</sub>D3 (Ma et al. Molecular and Cellular Endocrinology 2004; 221: 67-74). With regards to 1,25 (OH)<sub>2</sub>D3, Ma et al. teach that 1,25 (OH)<sub>2</sub>D3 has been shown to inhibit established prostatic cancer cell lines as well as primary culture of normal and malignant prostatic epithelial cells (page 67, 2<sup>nd</sup> column last paragraph to page 68, 1<sup>st</sup> column). Despite the anti-tumor activity of 1,25 (OH)<sub>2</sub>D3, Ma et al. teach that systemic hypercalcemia resulting from excessive circulation of 1,25 (OH)<sub>2</sub>D3 has limited its therapeutic potential and has led investigators to propose new strategies to harness the anti-tumor activity of 1,25 (OH)2D3 while circumventing hypercalcemic activity. For example, Ma et al. teach that this discovery has raised the possibility of intra-prostatic conversion of 25(OH)D3 to 1,25(OH)2D3 by endogenous 1a(OH)ase, allowing the use of the less hypercalcemic 25(OH)D3 instead of 1,25(OH)2D3 as a therapeutic approach (page 68, 1<sup>st</sup> column, 2<sup>nd</sup> paragraph). However, Ma et al. teach that 1a(OH)ase activity in human prostate cancer cells is dramatically reduced in comparison to cells derived from normal or benign prostatic hyperplasia (page 68, 1<sup>st</sup> column, 2<sup>nd</sup> paragraph). Similarly, Hsu et al. (Cancer Research 2001; 61: 2852-2856) quantified the levels of endogenous 1a-hydroxylase activity in a series of primary cultures of human prostatic epithelial cells derived from normal tissue, BPH, adenocarcinomas and several prostatic CA cell lines (page 2852, 2<sup>nd</sup> column, 3<sup>rd</sup> paragraph). Specifically, Hsu et al. found that CA cells had approximately 10 to 20 fold lower levels of 1 a-hydroxylase activity compared with cells from normal tissues (page 2852, 2<sup>nd</sup> column, 3<sup>rd</sup> paragraph). Likewise, Whitlatch et al. (J. Steroid Biochem. Molecular Biology 2002; 81: 135-140) compared the levels of 1a-OHase activity in prostate cancer cell lines, LNCaP, DU145 and PC-3 and in primary cultures of normal, cancerous and benign prostatic hyperplasia (BPH) prostate cells (abstract). In particular, Whitlatch et al. observed that compared to primary cultures of normal prostate cells, primary cultures of prostate cancer cells and prostate cancer cell lines demonstrate a marked decline in 1a-OHase activity (page 138, 2<sup>nd</sup> column, last paragraph and page 137, Figure 1). As such, both Hsu et al. and Ma et al teach that the proposed strategy of using 25(OH)D3 as a

therapeutic agent for prostate cancer will be ineffective (abstract or Hsu et al. and page 68, 1<sup>st</sup> column, 1<sup>st</sup> full paragraph of Ma et al.)

With regards to the unpredictability in the art, those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. In addition, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

**Conclusion**

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification for correlation in vitro results to in vivo success, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 20, 22-23, 25-27, 29-30 and 32-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Raina et al. (Br. J. Cancer 1991; 63: 463-465, *of record*).

Raina et al. teach a method of treating progressive low grade non-hodgkin's lymphoma comprising administering 1 µg oral alfalcacidol daily (abstract). Thus, while Raina et al. do not explicitly teach that lymphoma have a hydroxylase enzyme, e.g., 25-hydroxyvitamin D-1a-hydroxylase, for synthesizing 1,25-dihydroxyvitamin D from 25-hydroxyvitamin D, the claimed limitation does not appear to result in a manipulative difference when compared to the prior arts disclosure because the specification discloses (page 23, lines 11-24) that 1a-OHase is present in lymphoma cancer cells and synthesizes 1,25-dihydroxyvitamin D from 25-hydroxyvitamin D. Moreover, although Raina et al. do not explicitly teach that alfalcacidol is an analog or derivative of 25-hydroxyvitamin D, the claimed limitation does not appear to result in a manipulative difference between the prior art compound and the claimed derivative because the specification teaches that useful analogs, derivatives and salts of 25(OH)D include alkylated, glycosylated, arylated, halogenated, or hydroxylated 25(OH)D, orthoesters of 25(OH)D, or pharmaceutical salts of 25(OH)D (page 18, lines 25-28). As such, Raina et al.'s alfalcacidol appears to be a derivative of 25-

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hydroxyvitamin D, wherein the claimed 25-hydroxyvitamin D has been at least hydroxylated and/or alkylated. Hence, even though the claims are drawn to a mechanism by which a metabolite of 25-dihydroxyvitamin D, analog or derivative thereof is accumulated within the cells; the claimed method does not appear to distinguish over the prior art teaching of the same or nearly the same method. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

In order to expedite prosecution, the Examiner would like to address Applicants arguments pertaining to the rejection of claims 1, 3-4, 7-8, 10-11 and 14 under 35 USC 102 (b) to the extent applicable to the instant rejection. In response to the previous rejection, Applicants assert that alfacalcidol is, notably, 1-OH-vitamin D<sub>3</sub>, a synthetic form and/or prodrug of Vitamin D in which a hydroxyl (OH) group is added to vitamin D, wherein alfacalcidol is converted to 1,25-dihydroxyvitamin D by a different enzyme (25-Ohase) in the kidney resulting in the release of the compound into the systemic circulation. As such, Applicants assert that alfacalidol is fundamentally different from our discovery that the prostate and other cells possess 1-Ohase, and convert 25-hydroxyvitmain D to 1,25-dihydroxyvitamin D intraprostatically, e.g., within the cancerous organ, wherein the calcemic effects of 25-hydroxyvitamin D are much lower than that of 1,25 dihydroxyvitamin D and alfaclidiol.

These arguments have been carefully considered, but are not found persuasive.

Regarding Applicants arguments, the Examiner acknowledges that Applicants have discovered that the prostate and other cells possess 1-Ohase, and convert 25-hydroxyvitmain D to 1,25-dihydroxyvitamin D intraprostatically, wherein the calcemic effects of 25-hydroxyvitamin D are much lower than that of 1,25 dihydroxyvitamin D and alfaclidiol. However, the Examiner recognizes that Applicants appear to be arguing features which are not present in the instant claims. Although the claims are interpreted in light of the specification, limitations from the specification

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are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In the instant case, the claims recite a method of inhibiting tumor cells and/or cancer cells comprising administering a composition comprising an effective amount of 25-hydroxyvitamin D, or an analog, salt or derivative thereof, to increase the levels of a metabolite of said 25-dihydroxyvitamin D, or its said analog, salt or derivative in said tumor cells in a target organ, wherein the tumor cells have a hydroxylase enzyme for synthesizing 1,25-dihydroxyvitamin D from said 25-hydroxyvitamin D. As such, the active steps of the instant claims are administration of a composition comprising an effective amount of 25-hydroxyvitamin D, or an analog, salt or derivative thereof, to increase the levels of a metabolite of said 25-dihydroxyvitamin D, or its said analog, salt or derivative in said tumor cells in a target organ, wherein the functional characterization of the tumor cells possessing a hydroxylase enzyme would be an inherent feature of lymphoma cells, as evidenced by the specification. Thus, Raina et al.'s teachings of the active steps, as noted above, anticipates the claimed invention.

Claims 20, 22-27 and 29-33 are rejected under 35 U.S.C. 102(b) as being anticipated by Getzenberg et al. (Urology 1997; 50: 999-1006).

Getzenberg et al. teach a method of inhibiting prostate tumor and/or cancer growth in an animal, comprising administering 1,25-D3 and less-hypercalcemic analogues, Ro25-6760, to an animal (page 1003, Table II and IV). Thus, while Getsenberg et al. do not explicitly teach that prostate have a hydroxylase enzyme, e.g., 25-hydroxyvitmain D-1a-hydroxylase, for synthesizing 1,25-dihydroxyvitamin D from 25-hydroxyvitamin D, the claimed limitation does not appear to result in a manipulative difference when compared to the prior arts disclosure because the specification discloses (page 23, lines 11-24) that 1a-OHase is present in prostate cancer cells and synthesizes 1,25-dihydroxyvitamin D from 25-hydroxyvitamin D. Moreover, although Getzengerb et al. do not explicitly teach that 1,25-D3 is an analog or derivative of 25-hydroxyvitamin D, the claimed limitation does not appear to result in a manipulative difference between the prior art compound and the claimed derivative because the specification teaches that useful analogs, derivatives and salts of 25(OH)D include alkylated, glycosylated, arylated, halogenated, or hydroxylated 25(OH)D, orthoesters of 25(OH)D, or pharmaceutical salts of 25(OH)D (page 18,

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lines 25-28). As such, Getzenberg et al.'s 1,25-D<sub>3</sub> appears to be a derivative of 25-hydroxyvitamin D, wherein the claimed 25-hydroxyvitamin D has been at least hydroxylated. Hence, even though the claims are drawn to a mechanism by which a metabolite of 25-dihydroxyvitamin D, analog or derivative thereof is accumulated within the cells; the claimed method does not appear to distinguish over the prior art teaching of the same or nearly the same method. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

#### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 21 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Getzenberg et al. (Urology 1997; 50: 999-1006) in view of Haussler et al. (JAMA 1982; 247: 841-844, *of record*).

Getzenberg et al. teach, as applied to claims 20, 22-27 and 29-33 above, a method of inhibiting prostate tumor and/or cancer growth in an animal, comprising administering 1,25-D3, e.g., calcitriol, and less-hypercalcemic analogues, Ro25-6760, to an animal (page 1003, Table II and IV).

Getzenberg et al. does not explicitly teach that the administration of 25-hydroxyvitamin D as the metabolic precursor.

Hausslet et al. teach that while calcitriol is the most active natural metabolite of Vitamin D, analogs such as calcifediol (25-hydroxyvitamin D) are safe and effective alternative therapeutic agents to Vitamin D (abstract). Specifically, the reference teaches that calcifediol has become a useful alternative to Vitamin D because it is faster acting and assays for measuring its concentration are readily available such that its therapeutic levels can be easily monitored; and further, calcifediol has been shown to substitute for 1,25-D3, e.g., calcitriol, at receptor sites (page 843, 2<sup>nd</sup> column, *Calcifediol*).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute calcitriol as taught by Pence for 25-hydroxyvitamin D in view of Haussler et al. teachings that calcifediol, e.g., 25-hydroxyvitamin D, is recognized as a safe and effective alternative to Vitamin D. Moreover, one would have been motivated because as taught by Haussler, calcifediol is faster acting than vitamin D and its therapeutic levels can be easily monitored by readily available techniques; and further, calcifediol has been shown to substitute for 1,25-D3, e.g., calcitriol, at receptor sites. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering 25-hydroxyvitamin D, one would achieve a safe and effective alternative to 1,25-D3, e.g., calcitriol, for the treatment of colon cancer.

Therefore, No claim is allowed.

### ***Conclusion***

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US Patent 6,521,608 (2003), which claims a method of treating in a subject a tumor that expresses a Vitamin D receptor, the method comprising administering a dose of a Vitamin D drug

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to raise the blood level of the Vitamin D drug, wherein the Vitamin D drug is 25-hydroxyvitamin D3.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD  
Patent Examiner  
Art Unit 1642

  
SHANON FOLEY  
SUPERVISORY PATENT EXAMINER  
TECHNOLOGY CENTER 1600

